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A STEREOCONTROLLED FORMAL TOTAL SYNTHESIS OF (±)-THIENAMYCIN

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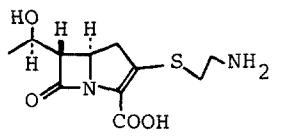
Abstract—The stereocontrolled synthesis of a key intermediate **20** for the preparation of (±)-thienamycin **1** is described. The key steps in the synthesis are the formation of the β-lactam ring by cyclization of the amide **5** via a complete S_N2 mechanism, and the stereospecific conversion of the azetidinone **5** to the amide (*trans*-**11**) which have the correct relative configurations at three contiguous chiral centres. The mechanism of the conversion of the azetidinone **16E** to the *N*-free azetidinone **17** and the selenide compound **18** is presumed.

Thienamycin **1**[1] is a broad-spectrum β-lactam antibiotic isolated recently from *Streptomyces cattleya* by a Merck research group.[2] It has high antibacterial activity against both gram-positive and gram-negative bacteria, including *Pseudomonas* spp. and is resistant to bacterial β-lactamase. The total syntheses of (±)- and (+)-thienamycin having a unique and synthetically challenging structure have been reported.[3] In the practical synthesis of thienamycin, there are four main problems requiring solutions; (i) the elaboration of the three contiguous chiral centres in a stereocontrolled manner, (ii) the construction of the carbapenem bicyclic system which is chemically less stable than the penem nucleus, (iii) the choice of a chiral starting material or the resolution of a racemic intermediate, and (iv) the choice of protecting groups for hydroxy, carboxy, amino, and amide groups. Two Merck research groups have already ingeniously solved these problems.[3a–g] We wish to report another stereocontrolled synthesis of (±)-thienamycin intermediates possessing the same relative configurations at the three chiral centres of thienamycin.[4]

(±) - *Erythro* - 2 - bromo - 3 - acetoxybutyric acid **2**[4] was treated with thionyl chloride in methylene chloride at reflux temperature for 8 hours to give the corresponding acid chloride **3**. This acid chloride **3** was found to be unstable when it was distilled, but fairly stable below 40°, hence **3** was used for the following reaction without distillation. Treatment of **3** with the lithium salt of the amine **4** obtained from the reaction of diethyl aminomalonate with *tert*-butyl bromoacetate gave the amide **5**. The amide **5** was cyclized to the β-lactam compound **6** on treatment with DBN in benzene at 80° for 1 hr. This β-lactam cyclization method had already been reported in a more simple compound by Sheehan and Bose[5] in 1950. In our case, this cyclization reaction proceeded smoothly not only in good yield, but also with complete inversion of the configuration in the intramolecular nucleophilic substitution reaction. During this reaction, the elimination reaction of the acetoxy group in which **5** should have been transformed to a 2-bromocrotonamide derivative did not occur. The relative configuration of **6** was confirmed from the ^{1}H NMR study of the lactone **7** which was easily obtained by the saponification of **6** with 3 equivalents of aqueous 1*N* NaOH and successive treatment with hydrochloric acid. The dihedral angle between the hydrogen (Ha) on the lactone ring and the bridge head hydrogen (Hb) is nearly 100°, and that between the methyl group on the lactone ring and Hb is approximately 10° when measured using a Dreidig molecular model for the lactone **7** with the desired stereochemistry. The observed coupling constant (J_{HaHb} = 1.5 Hz) supports the relative configuration of **7** as being correct.

Saponification of **6** with 1 quuivalent of aqueous 1*N* NaOH–pyridine (2:1) at 0° gave an acid **8**, m.p. 121–123°, in 50.5% yield from the amine **4**. Since the saponification would occur at the less hindered side, the C-4 carboxyl group of **8** should be *trans* to the C_3-acetoxyethyl group. Actually this trend was confirmed from another experiment in a closely related compound.[6] Decarboxylation of **8** with 1 equivalent of pyridine at 140–150° for one hour gave a mixture of *cis*- and *trans*-**9** (1:1, in 71% yield) which was separable chromatographically. Isomerization of *cis*-**9** to *trans*-**9** was not accomplished under the same conditions as that of the decarboxylation. This appears to indicate that the sp^3 carbon at the C-4 position of **8** was partly changed to the carbon possessing an sp^2 like orbital at the C-4 position of an intermediate, to afford *trans*-**9** in the course of the decarboxylation reaction. The ratio of *cis* and *trans* isomers altered largely according to both the substituents on the β-lactam nitrogen and that of the C-3 position, as we can understand from another experiment.[6] In fact, in a more simple compound, A. K. Bose recommends this decarboxylation method to provide an easy pathway for the stereospecific synthesis of *cis*-3,4-disubstituted-2-azetidinone.[7]

Saponification of **9** (*cis*:*trans* = 1:1) with 1 equivalent of aqueous 1*N* NaOH–pyridine (2:1) at 0° for 18 hr and then 20° for 6 hr gave a mixture of carboxylic acids (**10**, *cis*:*trans* = 3:4) in 77% yield, with recovery of *cis*-**9**, m.p. 79–81°, in 12% yield. The mixture of *cis*-**10** and *trans*-**10** (3:4) was treated with oxalyl chloride in tetrahydrofuran at 60° for 1 hr to give a mixture of acid chlorides which was converted in succession to the corresponding diazoketones with excess ethereal diazomethane and these diazoketones were further transformed to chloromethyl ketones with hydrochloric acid in tetrahydrofuran at 0° for 5 min. The chloromethyl ketones gave a mixture of phenylthiomethyl ketones **11** (*cis*:*trans* = 3:4) on treatment with thiophenol and



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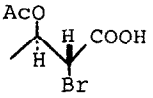
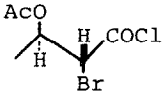


(±)- 2



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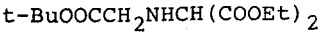

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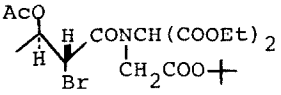

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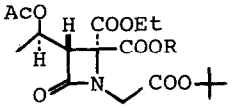
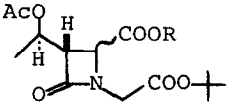


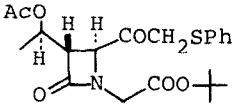
6 R=Et

8 R=H

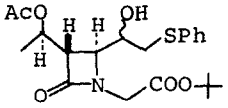


9 R=Et

10 R=H



trans 11



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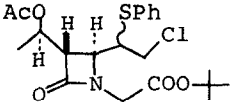

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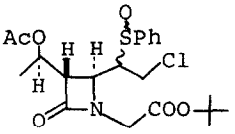

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Scheme 1.

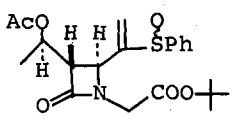
triethylamine at 20° in tetrahydrofuran for 15 hr. The same R_f value of *cis*-**11** and *trans*-**11** (development; benzene:ethyl acetate = 3:1) made it impossible to separate the isomers chromatographically. However, *cis*-**11** (m.p. 102–103.5°) was obtained from *cis*-**9** in the same successive procedures, or by fractional crystallization of *cis*-**11** and *trans*-**11** from diisopropyl ether. Equilibration of the *cis* and *trans* mixture of phenylthiomethyl ketones or that of the *cis* isomer with 1.1 equivalents of diazabicyclo(5,4,0)undecene in dimethylformamide at 25° for 1 hr formed *trans*-**11**, m.p. 91.5–92.5° (54.4% yield from **10**). However, a prolonged reaction time caused an increasing formation of a by-product, bis(phenylthio)methylketone.[4] The compound (*trans*-**11**) has the same relative configurations at the three chiral centres as thienamycin **1**.

Reduction of *trans*-**11** with $NaBH_4$ in ethanol at 0° for 20 min gave an epimeric mixture of alcohols **12**, quantitatively, which was impossible to separate chromatographically on a preparative silica gel tlc plate, due to the same R_f values of the two diastereoisomers. However, fractional crystallization of these diastereoisomers gave a crystalline solid of one racemate (m.p. 87–88°) from diisopropyl ether. The epimeric mixture of **12** was chlorinated with thionyl chloride in tetrhydrofuran at 20° for 10 hr to give a mixture of diastereoisomeric sulfides **13** (1:2 mixture, in 85% yield) which was obtained by the double migration of a chlorine atom and the phenylthio group via an intermediate thiiranium chloride. The regioisomer of **13** was not detected. Separation of the mixture of sulfides **13** by silica gel column chromatography gave a crystalline solid **13L** (m.p. 90.5–91.5°) from the lower R_f fractions, and an oil **13H** from the higher R_f fractions. Oxidation of **13L** with *m*-chloroperbenzoic acid gave two products (**14LH** and **14LL** in a ratio of 1.3:1) in 96% yield. The one having the higher R_f value, **14LH**, was a crystalline solid, m.p. 146.5–148°, and the one with the lower R_f value, **14LL**, was a foam. In addition, oxidation of **13H** yielded quantitatively a mixture of two sulfoxides, **14HH** (foam) and **14HL** (m.p. 174–180°), in the ratio 4.3:1. The former isomer (**14HH** showed a higher R_f value than that of the epimer **14HL** on a silica gel tlc plate. Oxidation of the mixture **13** without separation of each isomer (**13L** and **13H**) gave a mixture of four racemic isomers (**14HH**, **14HL**, **14LH**, and **14LL**) which was treated with diazabicyclo(5,4,0)undecene in benzene at 20° for 1 hr to afford a mixture of diastereoisomeric vinyl sulfoxides (**15** in 83% yield from **11**) revealing the same R_f values on a silica gel tlc plate. Michael type addition of the mixture **15** with *N*-tritylcysteamine, and

successive thermal phenyl sulfenic acid elimination gave two sulfides, **16E** (E-isomer) and **16Z** (Z-isomer), in 36% and 18% yield, respectively. The compound **16E** showed a higher R_f value than that of **16Z** on a silica gel tlc plate. Thermolysis of **14** in toluene gave two vinyl chlorides, **21E** and **21Z**, (E:Z = 2:1), in low yield. Treatment of **16E** with 2.3 equivalents of lithium hexamethyldisilazaide in tetrahydrofuran at −78° and successive addition of 2.8 equivalents of benzenseleninyl chloride,[8] and quenching with acetic acid–water gave the starting **16E** (12.5% recovery), **17** (33% yield) and **18** (11% yield) which were separated on a preparative silica gel tlc plate. In this reaction, there was no detection of selenoxide compounds. The structure of **18** was further confirmed as follows; treatment of **16E** with 1.2 equivalents each of lithium hexamethyldisilazaide and phenylselenyl chloride in tetrahydrofuran at −78° gave **18** in good yield.

The potentially useful thienamycin intermediate **17** was further converted into **20**. Deacetylation of **17** with aqueous 0.1*N* NaOH–pyridine (1:1) at 20° for 15 hr yielded an alcohol **19** besides the recovered starting material **17**. On the other hand, treatment of **19** with sodium methoxide in methanol at 0° for 1 hr gave a β-lactam ring fission product in good yield, without achieving the desired deacetylation.[4] Detritylation of **19** with trifluoroacetic acid in methylene chloride at 0° for 10 min, and further protection of the resulting aminoalcohol with *p*-nitrobenzyloxycarbonyl chloride and 4-dimethylaminopyridine in methylene chloride at reflux temperature for two hours gave the protected compound **20** which had already been correlated with thienamycin by Merck research groups.[3a-g] Here, we accomplished a stereocontrolled formal total synthesis of (±)-thienamycin.

We propose a tentative mechanism in order to rationalize the formation of **17** and **18** from **16E**. We believe that there was little contamination of phenylselenyl chloride in the used phenylseleninyl chloride.[8] In the first step, **16R** should be converted to the selenoxide **22** which might further be transformed to the selenonium ylide **23** via a geminal diselenoxide compound by reaction with **22** with excess base and seleninyl chloride. In this stage, Pummerer type rearrangement of **23** should occur to yield the benzeneseleninic ester **24**. As a general rule, esters of seleninic acids are marked by their very high sensitivity to water. Quenching of **24** with water may yield the *N*-deprotected product **17**. On the other hand, quenching of **23** with water might give the selenide **18** and benzeneselenonic acid by disproportionation reaction. Other experiments to prove this tentative mechanism have not been carried out, but this experiment was repeated four times using freshly prepared phenylseleninyl chloride.[8] Almost the same results were obtained from the series of trials except for the ratio of



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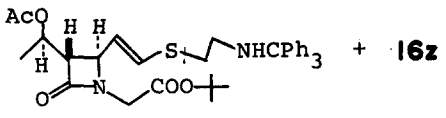
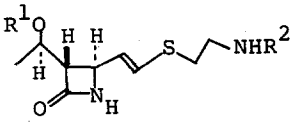


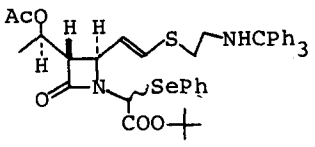
16E



17, R^1=Ac, R^2=CPh_3

19, R^1=H, R^2=CPh_3

20, R^1=R^2=$COOCH_2$-(p-NO_2)



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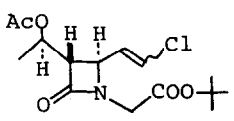
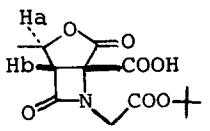


21E

21Z



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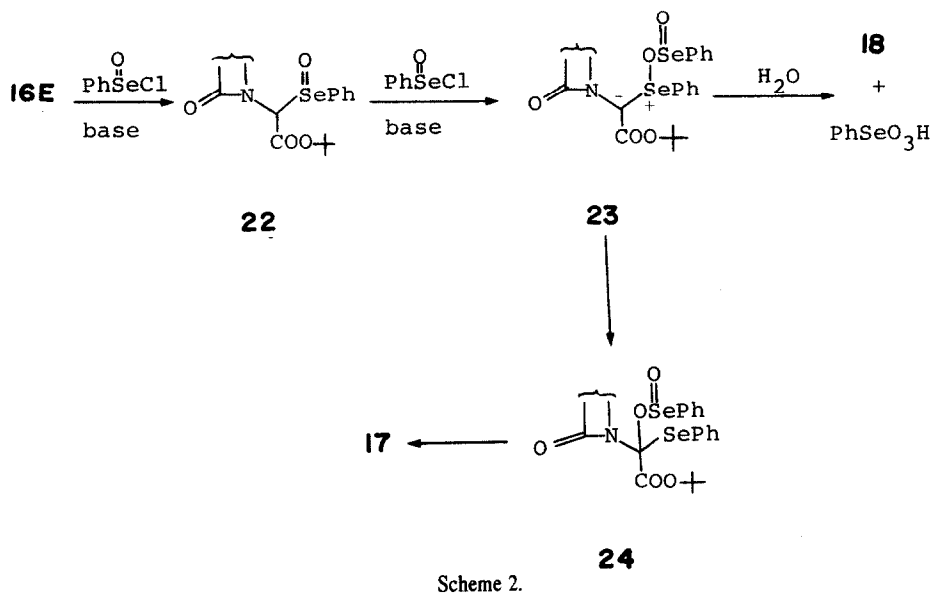

Scheme 2.

the yields of products **17** and **18** and the recovered starting **16E**.

EXPERIMENTAL

General. All m.ps are uncorrected. NMR were obtained on a Varian A-60 or HA-100 using TMS as an internal standard, IR spectra were recorded on a JASCO IR A-2 spectrophotometer, and mass spectra were taken on a JMS-01SG mass spectrometer. Preparative thin layer chromatography (preparative tlc) was carried out using Merck PF-254 silica gel.

(*R*,R**) - 2 - *Bromo* - 3 - *acetoxybutanoic acid* **2**. (a) A suspension of crotonic acid (86.1 g, 1.0 mol) and NBS (178 g, 1.0 mol) in AcOH (500 ml) was stirred for 5 days at room temp. AcOH was removed under reduced pressure at 45° and H_2O (2 l.) was added to the residual oil which was extracted with ether (500 ml × 3). The extract was washed with H_2O and sat. aq. NaCl, dried over $MgSO_4$, and evaporated to give 176 g of **2** (78.4% yield) as an oil: NMR (CD_3COCD_3) δ 1.46 (3H, d, J = 6 Hz), 2.07 (3H, s), 4.40 (1H, d, J = 7.5 Hz), 5.34 (1H, m). (b) To a soln of (**R*,R***)-2-bromo-3-hydroxybutanoic acid[9] (18.3 g, 0.10 mol) and AcCl (20 g, 0.255 mole) in CH_2Cl_2 (100 ml) was added dropwise a soln of pyridine (17.4 g, 0.22 mole) in CH_2Cl_2 (100 ml) over 1 h at 0–5°. The reaction mixture was stirred for 1.5 h at 5°, acidified with dil. HCl, and extracted with ether. The extract was washed with H_2O, and evaporated to give an oily mixture which was stirred with THF-H_2O (1:1, 100 ml) at room temp. for 4 h to hydrolyze the acid anhydride of **2**. The resulting soln was extracted with ether which was dried over $MgSO_4$, and evaporated to give 20.0 g of **2** as an oil.

(*R*,R**) - 2 - *Bromo* - 3 - *acetoxybutyryl chloride* **3**. To a soln of **2** (170 g, 0.755 mol) in CH_2Cl_2 (600 ml) was added gradually $SOCl_2$ (330 g, 2.77 mol). The mixture was refluxed for 8 h, and evaporated under reduced pressure at less than 40°. To the residual oil was added benzene (100 ml × 2), and evaporation was repeated twice in order to remove the excess $SOCl_2$. The oil was then dried with a pump to give 184 g of **3**. This acid chloride was used in the next reaction without distillation which caused a fair amount of decomposition of **3**. NMR ($CDCl_3$) δ 1.45 (3H, d, J = 6.5 Hz), 2.06 (3H, s), 4.68 (1H, d, J = 8 Hz), 5.30 (1H, m).

N - *Bis(carboethoxy)methyl* - N - tert - *butoxycarbonylmethylamine* **4**. To a suspension of diethyl aminomalonate HCl (127 g, 0.60 mol) in THF (1.5 l.) was added *t*-butyl bromoacetate (235 g, 1.20 mol) and Et_3N (134 g, 1.32 mol). This mixture was refluxed for 5 h with stirring. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo* to give an oil which was diluted with EtOAc. The soln was washed with H_2O, sat. $NaHCO_3$, and sat. NaCl, and dried over $MgSO_4$. Evaporation of EtOAc gave an oil which was chromatographed on a silica gel (1.25 kg) column. Elution with benzene (4 l.) recovered *t*-butyl bromoacetate (32 g), and that with PhH–EtOAc (3:1, 6 l.) gave 81 g of **4**; NMR ($CDCl_3$) δ 1.27 (6H, t, J = 7 Hz), 1.43 (9H, s), 2.38 (1H, bs, NH), 3.28 (2H, s), 3.93 (1H, s), 4.20 (4H, q, J = 7 Hz); IR ν_{max} (film) 1735, 1365, 1150, 1025 cm^{-1}.

(*R*,R**) - N - Bis(*carboethoxy*)*methyl* - N - tert - *butoxycarbonylmethyl* - 2 - *bromo* - 3 - *acetoxybutylamide* **5**. To a soln of **4** (9.64 g, 33.3 mmol) in dry THF (100 ml) was added gradually *n*-butyl lithium (15% soln in *n*-hexane, 20.4 ml, 33.3 mmol) in THF (50 ml) at −78° under a nitrogen atmosphere to afford the corresponding lithium salt of **4**, and to the resulting soln, **3** (8.12 g, 33.3 mmol) in THF (50 ml) was added at once with vigorous stirring. After a reaction time of 1 h at −78°, the reaction mixture stood for 18 h at 25°, and poured into 5% HCl, and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated to give an oil which was chromatographed on silica gel (250 g, eluate; PhH/EtOAc = 95/5) to produce **5** (10.87 g, 66% yield); IR ν_{max} (film) 1745, 1685 (shoulder), 1677 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (6H, t, J = 7 Hz), 1.42 (9H, s), 1.42 (3H, d, J = 6 Hz), 1.97 (3H, s), 4.00–4.42 (7H, m), 5.27 (1H, m), 5.88 (1H, s).

(*R*,S**) - 1 - t - *Butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4,4 - bis - (*ethoxycarbonyl*) - 2 - *azetidinone* **6**. To a soln of **5** (10.87 g, 21.8 mmol) in benzene (100 ml), 1,5-diazabicyclo(4,3,0)non-5-ene (2.70 g, 21.8 mmol) was added. The mixture was heated at 80° for 1 h (during which DBN·HBr salt was deposited), and diluted with EtOAc (100 ml), washed with 10% HCl aq., sat. $NaHCO_3$, sat. NaCl, dried over $MgSO_4$, and evaporated to give 8.84 g of **6** as an oil (99% yield). An analytical sample was purified on a preparative tlc plate (silica gel, 60 F_{254} pre-coated, 20 × 20 × 2, Merck). IR ν_{max} (film) 1787, 1742 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7 Hz), 1.36 (3H, d, J = 6.5 Hz), 1.39 (9H, s), 1.93 (3H, s), 3.73, 4.25 (2H, AB-q, J = 18.5 Hz), 3.8–4.4 (5H, m), 5.19 (1H, qd, J = 6.5, 8.5 Hz); MS *m/e* 415 (M^+), 359 ($M^+ - C_4H_8$), 341, 315. (Found: C, 54.61; H, 7.28; N, 3.12. $C_{19}H_{29}O_9N$ requires: C, 54.93; H, 7.04; N, 3.37%).

[3α(*S**),4α] - 1 - tert - *Butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - *ethoxycarbonyl* - 2 - *azetidinone* - 4 - *carboxylic acid* **8**. A soln of **6** (4.15 g, 10 mmol) in pyridine (5 ml) and 1*N* NaOH (10.5 ml) stood for 18 h at 0°. This reaction mixture was diluted with sat. $NaHCO_3$ (20 ml) and washed with EtOAc. The aqueous layer was acidified with 10% HCl, and extracted with EtOAc. The extract was washed with H_2O and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give two acids which were separated by column chromatography using silica gel (eluant; PhH/EtOAc = 7/3) to give 1.74 g (45% yield) of **8** as a crystalline solid; m.p. 121–123° (from ether-*n*-

hexane); IR ν_{max} (nujol) 1773, 1750, 1720 (shoulder) cm^{-1}; NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7 Hz), 1.36 (3H, d, J = 6.5 Hz), 1.38 (9H, s), 1.92 (3H, s), 3.5–4.3 (5H, m), 5.09 (1H, qd, J = 6.5, 9 Hz), 9.10 (1H, bs); MS m/e 287 (M^+). Found: C, 52.73; H, 6.48; N, 3.64. $C_{17}H_{25}O_9N$ requires: C, 52.71; H, 6.51; N, 3.62%), and 0.23 g (7.7% yield) of a lactone carboxylic acid **7** as a crystalline solid; m.p. 152.5–154.5° (decomp) (from EtOAc); IR ν_{max} (nujol) 3200–2400, 1778, 1762, 1740, 1712 cm^{-1}; NMR (CD_3COCD_3) δ 1.44 (9H, s), 1.53 (3H, d, J = 6.5 Hz), 3.87, 4.21 (2H, AB-q, J = 18 Hz), 4.13 (1H, d, J = 1.5 Hz), 5.00 (1H, qd, J = 6.5, 1.5 Hz), 9.70 (1H, bs, COOH). (Found: C, 52.13; H, 5.71; N, 4.70. $C_{13}H_{17}O_7N$ requires: C, 52.17; H, 5.73; N, 4.68%).

(1α,4α,5α) - 2,6 - *Dioxo* - 4 - *methyl* - 7 - tert - *butoxycarbonylmethyl* - 3 - *oxa* - 7 - *azabicyclo*(3,2,0)*heptane* - 1 - *carboxylic acid* **7**. A mixture of **8** (387.4 mg, 1.0 mmol) in pyridine (1.6 ml) and 1*N* NaOH (3.2 ml) was stood for 18 h at 25°. This reaction mixture was diluted with sat. $NaHCO_3$ (10 ml) and washed with Et_2O. The aqueous layer was acidified with conc. HCl, and extracted with EtOAc. The extract was washed with H_2O and sat. NaCl, dried over $MgSO_4$, and evaporated to give 272 mg of **7** (91% yield).

A mixture of [3α(*S**),4α]- *and* [3α(*S**),4β] - 1 - tert - *Butoxycarbonylmethyl* - 4 - *ethoxycarbonyl* - 3 - (1 - *acetoxyethyl*) - 2 - *azetidinone* **9** (cis-9) and (trans-9). A mixture of **8** (387 mg, 1 mmol) and pyridine (80 mg) was heated at 140° for 1 h with stirring. The reaction mixture was diluted with EtOAc (30 ml), washed with 5% HCl aq., sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give 312 mg of **9** (*cis*:*trans* = 1:1 mixture, from proton NMR); MS m/e 343 (M^+), 287 ($M^+ - C_4H_8$); IR ν_{max} (film) 1775, 1742 cm^{-1}.

[3α(*S**),4α]- *and* [3α(*S**),4β] - 1 - tert - *butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 2 - *azetidinone* - 4 - *carboxylic acid* **10** (cis-**10**) *and* (trans-**10**). (a) A soln of **9** (25.5 g, *cis*:*trans* = 1:1) in pyridine (37 ml) and 1*N* NaOH (74 ml) stood for 15 h at 0°C, and was stirred for 6 h at 25°. This reaction mixture was diluted with sat. $NaHCO_3$ (20 ml) and washed with EtOAc to remove unreacted starting material and pyridine. The aqueous layer was acidified with conc. HCl, and extracted with EtOAc. The extract was washed with H_2O and sat. NaCl, dried over $MgSO_4$, and evaporated to give 17.3 g of *cis*-**10** and *trans*-**10** (74% yield, *cis*:*trans* = 3:4); IR ν_{max} (film) 3600–2400 (w), 1775 (shoulder), 1740, 1720 (shoulder) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (3H, d, J = 6 Hz), 1.40 (9H, s), 1.91 (*trans* isomer, 1.7H, s, $OCOCH_3$), 1.99 (*cis* isomer, 1.3H, s, $OCOCH_3$), 3.5–5.5 (5H, m), 8.87 (1H, bs, COOH). The only starting material recovered was *cis*-**9** (4.9 g, 19.3% recovery) as a crystalline solid; mp 79–81° (from EtOAc-*n*-hexane); IR ν_{max} (nujol) 1760, 1730, 1722 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7 Hz), 1.30 (3H, d, J = 6 Hz), 1.38 (9H, s), 1.89 (3H, s), 3.55, 4.26 (2H, AB-q, J = 18 Hz), 3.63 (1H, dd, 5.5, 9.5 Hz), 4.10 (2H, q, J = 7 Hz), 4.49 (1H, d, J = 5.5 Hz), 5.10 (1H, dq, J = 9.5, 6 Hz). (Found: C, 56.06; H, 7.37; N, 3.90. $C_{16}H_{25}O_7N$ requires: C, 55.96; H, 7.34; N, 4.08%). (b) A soln of *cis*-**9** (341 mg, 1 mmol) in pyridine (5.5 ml) and 0.1*N* NaOH (11 ml) stood for 15 h at 25°C. The reaction mixture was treated as described above to give 232 mg of *cis*-**10** (73.6% yield).

[3α(*S**),4α]- *and* [3α(*S**),4β] - 1 - tert - *Butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - (1 - *oxo* - 2 - *phenylthioethyl*) - 2 - *azetidinone* (cis-**11**) *and* (trans-**11**). (a) To a soln of **10** (*cis*:*trans* = 3:4 mixture, 315 mg, 1 mmol) in THF (3 ml) was added oxalyl chloride (0.15 ml, 1.76 mmol) with stirring at 25°. The mixture was heated at 60° for 1.5 h, and evaporated to give an oily mixture of acid chlorides. The mixture was dissolved in THF (5 ml) and poured into an excess ethereal CH_2N_2 soln at 0°. After 1 h stirring at 25°, evaporation of the solvent under reduced pressure gave a mixture of two diazomethylketones and two chloromethylketones. This mixture was dissolved in THF (10 ml), treated with dry HCl at 0° for 5 min, and diluted with EtOAc. The soln was washed with sat. $NaHCO_3$, dried over $MgSO_4$, and evaporated to give an oily mixture of chloromethylketones. A soln of this oil in THF (10 ml) was treated with thiophenol (120 mg) and Et_3N (110 mg) at 25° for 18 h. This reaction mixture was diluted with EtOAc, washed with 10% HCl aq., sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily mixture. This residual oil was purified on a silica gel preparative tlc plate (developed with PhH/EtOAc = 4/1) to give 276 mg of a *cis*- and *trans*-**11** mixture (*cis*:*trans* = 3:4) in 65.5% yield. Fractional crystallization of this mixture from *iso*-Pr_2O gave *cis*-**11** as a crystalline solid and a *trans*-**11** rich mother liquor. (b) Successive treatment of *cis*-**10** (100 mg, 0.316 mmol) as described above gave 56 mg of *cis*-**11** (42% yield) as a crystalline solid; m.p. 102–103.5° (from *iso*-Pr_2O); NMR ($CDCl_3$) δ 1.32 (3H, d, J = 6.5 Hz), 1.40 (9H, s), 1.90 (3H, s), 3.25, 4.20 (2H, AB-q, J = 18.5 Hz), 3.64 (1H, dd, J = 6, 10 Hz), 3.65 (2H, s), 4.86 (1H, qd, J = 6.5, 10 Hz), 4.98 (1H, d, J = 6 Hz), 7.32 (5H, s); IR ν_{max} (nujol) 1780, 1744, 1712 cm^{-1}. (Found: C, 59.55; H, 6.45; N, 3.02; S, 7.76. $C_{21}H_{27}O_6NS$ requires: C, 59.85; H, 6.46; N, 3.32; S, 7.59%).

[3α(*S**),4β] - 1 - tert - *Butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - (1 - *oxo* - 2 - *phenylthioethyl*) - 2 - *azetidinone* (trans-**11**). (a) To a soln of *cis*-**11** (35 mg) in DMF (1 ml) was added 1,8-diazabicyclo(5,4,0)undec-7-ene (DBU, 13 mg) at 25°. After 1 h stirring, the mixture was diluted with EtOAc, washed with 10% HCl and aq. sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily residue. The residual oil was purified on a silica gel preparative tlc plate (developed with PhH/EtOAc = 4/1) to give 29 mg of *trans*-**11** (83% yield); m.p. 91.5–92.5° (from EtOAc-*n*-hexane); IR ν_{max} (nujol) 1765, 1750, 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3H, d, J = 6.5 Hz), 1.40 (9H, s), 2.01 (3H, s), 3.13 (1H, dd, J = 2.5, 8 Hz), 3.53, 4.22 (2H, AB-q, J = 19 Hz), 3.71 (2H, s), 4.75 (1H, d, J = 2.5 Hz), 5.24 (1H, qd, J = 6.5, 8 Hz), 7.32 (5H, s); MS m/e 421 (M^+), 365 ($M^+ - C_4H_8$), 320, 305. (Found: C, 59.89; H, 6.61; N, 3.11; S, 7.68. $C_{21}H_{27}O_6NS$ requires: C, 59.85; H, 6.46; N, 3.32; S, 7.59%). (b) Treatment of a mixture of *cis*-**11** and *trans*-**11** (421 mg, 1 mmol, *cis*/*trans* = 3/4) in DMF (6 ml) with DBU (170 mg, 1.12 mmol) as described above, gave 334 mg of *trans*-**11** (79% yield) and 14 mg of [3α(S*),4β] - 1 - *tert* - butoxycarbonylmethyl - 3 - (1 - acetoxyethyl) - 4 - [1 - oxo - 2,2 - bis(phenylthio)ethyl] - 2 - azetidinone (2.6% yield) as an oily by-product; IR ν_{max} (film) 1775, 1740, 1582 cm^{-1}; MS m/e 529 (M^+), 473 ($M^+ - C_4H_8$); NMR ($CDCl_3$) δ 1.38 (3H, d, J = 6.5 Hz), 1.49 (9H, s), 1.92 (3H, s), 3.00 (1H, dd, J = 2.5, 7 Hz), 3.43, 4.32 (2H, AB-q, J = 18 Hz), 4.85 (1H, d, J = 2.5 Hz), 5.06 (1H, s), 5.28 (1H, qd, J = 6.5, 7 Hz), 7.47 (10H, m).

A mixture of [3α(*S**),4β(*S**)]- *and* [3α(*S**),4β(*R**)] - 1 - tert - *butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - (1 - *hydroxy* - 2 - *phenylthioethyl*) - 2 - *azetidinone* **12**. To a soln of *trans*-**11** (421 mg, 1 mmol) in EtOH (99.5%, 20 ml) was added $NaBH_4$ (25 mg, 0.678 mmol) at 0° with stirring. After a reaction time of 20 min at 0°, the reaction mixture was acidified with 10% HCl aq., and diluted with EtOAc (200 ml). The soln was washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evapoated under reduced pressure to give 423 mg of a mixture of diastereoisomers **12** (100% yield), having the same R_f values of 0.325 (developed with PhH/EtOAc = 4/1) as oily products. Fractional crystallization from *iso*-Pr_2O gave one isomer as a crystalline solid; m.p. 87–88°; IR ν_{max} (nujol) 3420, 1773, 1733, 1710, 1590 (w) cm^{-1}; MS m/e 423 (M^+); NMR ($CDCl_3$) δ 1.40 (3H, d, J = 6 Hz), 1.45 (9H, s), 2.02 (3H, s), 2.86 (1H, dd, J = 8, 14 Hz), 3.20 (1H, dd, J = 6, 14 Hz), 3.48, 4.33 (2H, AB-q, J = 18 Hz), 3.52 (1H, dd, J = 2, 10 Hz, C_3-H), 3.83 (1H, dd, J = 2, 6 Hz, C_4-H), 3.80 (1H, s, OH), 4.53 (1H, ddd, J = 6, 6, 8 Hz), 5.20 (1H, qd, J = 6, 10 Hz), 7.30 (5H, m).

A mixture of [3α(*S**),4β(*S**)]- *and* [3α(*S**),4β(*R**)] - 1 - tert - *butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - (1 - *phenylthio* -2-*chloroethyl*)-2-*azetidinone* **13**. **13H** and **13L**. A mixture of **12** (360 mg, 0.85 mmol), Na_2CO_3 (1.0 g) and $SOCl_2$ (0.3 ml, 4.1 mmol) in THF (5 ml) was stirred for 6 h at 25°, poured into H_2O, and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily residue **13**. Separation of the residual oil by preparative tlc on silica gel (developed with PhH/EtOAc = 4/1) gave two stereoisomers: the major and polar isomer **13L** (210 mg, 55.8% yield, R_f = 0.57); m.p. 90.5–91.5° (from *iso*-Pr_2O); NMR ($CDCl_3$) δ 1.37 (3H, d, J = 6.5 Hz), 1.42 (9H, s), 1.98 (3H, s), 3.36 (1H, dd, J = 2, 9 Hz, C_3-H), 3.55–3.75 (2H + 1H, m), 3.80, 4.26 (2H, AB-q, J = 18 Hz), 4.10 (1H, dd, J = 2, 6 Hz, C_4-H), 5.24 (1H, qd, J = 6.5, 9 Hz), 7.41 (5H, m).

(Found: C, 57.09; H, 6.43; N, 3.19; S, 7.41; Cl, 7.76. $C_{21}H_{28}O_5NSCl$ requires: C, 57.08; H, 6.39; N, 3.17; S, 7.25; Cl, 8.02%): and the minor and less polar isomer **13H** (108 mg, 28.7% yield, $R_f = 0.64$) as an oil; NMR ($CDCl_3$) δ 1.38 (3H, d, J = 6.5 Hz), 1.40 (9H, s), 2.02 (3H, s), 3.19, 4.11 (2H, AB-q, J = 18 Hz), 3.32 (1H, dd, J = 2.5, 9 Hz, C_3-H), 3.54–3.77 (2H + 1H, m), 4.36 (1H, dd, J = 2.5, 5.5 Hz, C_4-H), 5.23 (1H, qd, J = 6.5, 9 Hz), 7.42 (5H, m). (Found: C, 57.14; H, 6.54; N, 3.14; S, 7.41; Cl, 7.93. $C_{21}H_{28}O_5NSCl$ requires: C, 57.08; H, 6.39; N, 3.17; S, 7.25; Cl, 8.02%).

A mixture of [3α(*S**),4β(*S**,*S**)]- *and* [3α(*S**),4β(*S**,*R**)]- *or* [3α(*S**),4β(*R**,*S**)]- *and* [3α(*S**),4β(*R**,*R**)] - 1 - tert - *butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - (1 - *phenylsulfinyl* - 2 - *chloroethyl*) - 2 - *azetidinone* **14**. **14HH** *and* **14HL** *or* **14LH** *and* **14LL**. (a) To a soln of **13L** (155 mg, 0.35 mmol) in $CHCl_3$ (4 ml), was added *m*-chloroperbenzoic acid (70 mg, purity 85%, 0.35 mmol) at 0° with stirring. After a reaction time of 30 min, the reaction mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily mixture of **14LH** and **14LL**. Separation of the residual oil by preparative tlc on silica gel (developed with PhH/EtOAc = 4/1) gave two stereoisomers: the major and less polar isomer **14LH** (87 mg, 54% yield, R_f = 0.270); m.p. 146.5–148° (needles, from *iso*-Pr_2O–EtOAc); IR ν_{max} (nujol) 1767, 1747, 1740 cm^{-1}; (Found: C, 55.14; H, 6.14; N, 3.16; S, 7.12; Cl, 7.50. $C_{21}H_{28}O_6NSCl$ requires: C, 55.08; H, 6.16; N, 3.06; S, 7.00; Cl, 7.74%): and the minor and polar isomer (**14LL**, 68 mg, 42% yield, R_f = 0.123) as an oil; IR ν_{max} (film) 1770, 1738 cm^{-1}; MS *m/e* 401 ($M^+ - C_4H_8$). (b) The compound **13H** (78 mg, 0.18 mmol) was treated as described in (a) to give two stereoisomers: the major and less polar isomer (**14HH**, 65 mg, 80.5% yield, R_f = 0.221) as an oil; IR ν_{max} (film) 1770, 1738 cm^{-1}; MS *m/e* 401 ($M^+ - C_4H_8$): and the minor and polar isomer (**14HL**, 15 mg, 18.7% yield, R_f = 0.123) as a crystalline solid; m.p. 174–180° (from *iso*-Pr_2O–EtOAc); IR ν_{max} (nujol) 1772, 1739, 1737 (shoulder) cm^{-1}. (Found: C, 55.02; H, 6.15; N, 3.19. $C_{21}H_{28}O_6NSCl$: C, 55.08; H, 6.16; N, 3.06%). (c) The mixture of **13** (4.42 g, 10 mmole) was treated with *m*-chloroperbenzoic acid (2.04 g, purity 85%, 10 mmol) as described in (a) to give 4.45 g of a mixture of four stereoisomers **14** (97% yield).

A diasteroisomeric mixture of [3α(*S**),4β(*S**)]- *and* [3α(*S**),4β(*R**)] - 1 - tert - *butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - (1 - *phenylsulfinylvinyl*) - 2 - *azetidinone* **15**. To a soln of **14** (100 mg, 0.218 mmol) in THF (2 ml) was added DBU (35 mg, 0.23 mmol) with stirring at 25°. After a reaction time of 1 h, the reaction mixture was diluted with EtOAc, washed with 10% KH_2PO_4 aq. and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give 90 mg of **15** (97% yield); IR ν_{max} (film) 1770, 1740 cm^{-1}; NMR ($CDCl_3$) δ 6.03 (1H, bs, olefinic), 6.30 (1H, bs, olefinic). This was then used in the next reaction without further purification.

[3α(*S**),4β(*E*)]- *and* [3α(*S**),4β(*Z*)] - 1 - tert - *Butoxycarbonylmethyl* - 3 - (1 - *acetoxyethyl*) - 4 - [2 - (2 - *tritylaminoethyl*)*thiovinyl*] - 2 - *azetidinone* **16E** *and* **16Z**. To a soln of **15** (170 mg, 0.405 mmol) and *N*-tritylcysteamine (200 mg. 0.625 mmol) in benzene (5 ml) was added 1,5-diazabicyclo(4,3,0)non-5-ene (DBN, 55.5 mg, 0.445 mmol) with stirring at 0°. After a reaction time of 5 min, the reaction mixture was purified by column chromatography on silica gel (6 g). Elution with benzene removed excess *N*-tritylcysteamine, and elution with PhH–EtOAc (1:1) gave 270 mg of oily residue which was dissolved in toluene (5 ml) and heated with Na_2CO_3 (100 mg) for 1 h at reflux temperature. The reaction mixture was diluted with EtOAc, washed with H_2O and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give a mixture of two oily products. The mixture was separated by preparative tlc on silica gel to give 90 mg of **16E** (36.5% yield, R_f = 0.59, developed with PhH/EtOAc = 4/1); IR ν_{max} (film) 1770, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3H, d, J = 6.5 Hz), 1.40 (9H, s), 1.86 (1H, bs, NH), 1.95 (3H, s), 2.35 (2H, m), 2.78 (2H, m), 2.90 (1H, dd, J = 2, 7.5 Hz, C_3-H), 3.29, 3.95 (2H, AB-q, J = 18 Hz), 4.13 (1H, dd, J = 2, 9 Hz, C_4-H), 5.25 (1H, m), 5.37 (1H, dd, J = 9, 15 Hz), 6.23 (1H, d, J = 15 Hz), 7.33 (15H, m); MS *m/e* 614 (M^+); and 45 mg of **16Z** (18.2% yield, R_f = 0.52); IR ν_{max} (film) 1765, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (3H, d, J = 6.5 Hz), 1.38 (9H, s), 1.97 (3H, s), 2.25 (1H, bs, NH), 2.4–2.9 (2H + 2H, m), 3.08 (1H, dd, J = 2, 7.5 Hz, C_3-H), 3.47, 4.07 (2H, AB-q, J = 18 Hz), 4.52 (1H, dd, J = 2, 9.5 Hz, C_4-H), 5.34 (1H, m), 5.52 (1H, t, J = 9.5 Hz, olefinic), 6.27 (1H, d, J = 9.5 Hz, olefinic), 7.15–7.75 (15 H, m).

A mixture of [3α(*S**),4β(*E*),1(*R**)]- *and* [3α(*S**),4β(*E*),1(*S**)] - 1 - [(tert - *butoxycarbonyl*)(*phenylselenyl*)*methyl*] - 3 - (1 - *acetoxyethyl*) - 4 - [2 - (2 - *tritylaminoethyl*)*thiovinyl*] - 2 - *azetidinone* **18**. To a soln of 1,1,1,3,3,3,-hexamethyldisilazane (154 mg, 0.95 mmol) in THF (3 ml) was added 0.95 mmol of 1.6 *M* *n*-BuLi in *n*-hexane over 1 min under nitrogen atmosphere at 0°. After 5 min stirring, **16E** (234 mg, 0.38 mmol) in THF (3 ml) was added to this soln at −78°. After 10 min, phenylselenyl chloride (182 mg, 0.95 mmol) was added. After stirring at −78° for 30 min, the reaction mixture was diluted with EtOAc, washed with $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily residue. This was purified on a preparative silica gel tlc plate (developed with PhH/EtOAc = 9/1) to give 151 mg of **18** (51.5% yield) as a mixture of the two diastereoisomeric selenides in a ratio of 5:4 which was estimated from ^1H NMR: IR ν_{max} (film) 1760, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.07, 1.21 (each 3H, d, J = 6 Hz), 1.32, 1.34 (each 9H, s), 1.79, 1.86 (each 3H, s, $OCOCH_3$), 1.93, 2.00 (each 1H, bs, NH), 2.1–2.6 (2H, 2H, m), 2.6–3.0 (2H + 1H, 2H + 1H, m), 3.9–4.9 (1H + 1H, 1H + 1H, m), 4.9–5.6 (1H + 1H, 1H + 1H, m) 5.62, 5.78 (each 1H, s), 6.21, 6.33 (each 1H, d, J = 15 Hz), 7.1–7.7 (20H, 20H, m).

A mixture of [3α(*S**),4β(*Z*),1(*R**)]- *and* [3α(*S**),4β(*Z*),1(*S**)]- 1 - [(tert-*butoxycarbonyl*)(*phenylselenyl*)*methyl*] - 3 - (1 - *acetoxyethyl*) - 4 - [2 - (2 - *tritylaminoethyl*)*thiovinyl*] - 2 - *azetidinone* **18Z**, **16Z** (170 mg) was treated as described above to give 27 mg of the recovered starting material and 69 mg of **18Z** (34% yield); IR ν_{max} (film) 1760, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.10, 1.25 (each 3H, d, J = 6 Hz), 1.35 (9H, 9H, s), 1.84, 1.91 (each 3H, s, $OCOCH_3$), 2.10 (1H, 1H, s, NH), 2.25–2.55 (2H, 2H, m), 2.60–3.05 (2H + 1H, 2H + 1H, m), 4.25–4.80 (1H + 1H, 1H + 1H, m), 5.0–6.3 (3H, 3H, m), 7.1–7.8 (20H, 20H, m).

[3α(*S**),4β(*E*)] - 3 - (1 - *acetoxyethyl*) - 4 - [2 - (2 - *trityl-aminoethyl*)*thiovinyl* - 2 - *azetidinone* **17**. To a soln of 1,1,1,3,3,3 - hexamethyldisilazane (121 mg, 0.750 mmol) in THF (3 ml) was added with stirring 0.752 mmol of 1.6 *M* *n*-butyllithium in *n*-hexane at 0° under nitrogen atmosphere. After a reaction time of 5 min, the soln was cooled to −78° and **16E** (200 mg, 0.325 mmol) in THF (3 ml) was added. After stirring for 10 min, phenylseleninyl chloride (190 mg, 0.92 mmol) in THF (3 ml) was added at −78°. The soln was quenched with AcOH (0.5 ml), diluted with EtOAc, washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily mixture which was separated on a preparative silica gel plate. Development with PhH–EtOAc (9:1) gave 25 mg of the starting **16E** (12.5% recovery, R_f = 0.237), 27 mg of **18** (10.8% yield, R_f = 0.541), and 54 mg of **17** (33% yield, R_f = 0.068) as foam: IR ν_{max} (film) 3300, 1760, 1740, 1600 cm^{-1}; MS *m/e* 500 (M^+); NMR ($CDCl_3$) δ 1.28 (3H, d, J = 6.5 Hz), 1.43 (1H, s, NHTr), 1.95 (3H, s), 2.2–2.5 (2H, m), 2.6–2.9 (2H, m), 2.89 (1H, dd, J = 2, 7.5 Hz, C_3-H), 4.03 (1H, dd, J = 2, 7 Hz, C_4-H), 5.24 (1H, m), 5.50 (1H, dd, J = 7, 15 Hz), 6.21 (1H, d, J = 15 Hz), 7.72 (15H, m).

[3α(*S**),4β(*E*)] - 3 - (1 - *hydroxyethyl*) - 4 - [2 - (2 - *trityl-aminoethyl*)*thiovinyl* - 2 - *azetidinone* **19**. A soln of **17** (50 mg, 0.10 mmol) in 0.1 *N* NaOH aq.-pyridine (1:1, 1.1 ml) was stirred at 20° for 15 h, and extracted with EtOAc, washed with 5% HCl and aq. sat. NaCl, dried over $MgSO_4$, and evaporated under reduced pressure to give an oily mixture. Separation of this residue on a preparative silica gel tlc plate (developed with cyclohexane/EtOAc = 1/1) gave 27 mg of the starting **17** (54% recovery, R_f = 0.530) and 10 mg of **19** (22% yield, R_f = 0.206): IR ν_{max} (film) 3375, 1750, 1490, 1448 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6 Hz), 2.25 (2H, bs, NH, OH), 2.2–2.4 (2H, m), 2.68–2.91 (2H + 1H, m), 4.0–4.4 (1H + 1H, m), 5.51 (1H, dd, J = 7.5, 16 Hz), 6.09 (1H, bsm CONH), 6.20 (1H, d, J = 16 Hz), 7.15–7.60 (15H, m).

[3α(*S**),4β(*E*)] - 3 - (1 - *p* - *nitrobenzyloxycarbonyloxyethyl*) - 4 - [2 - (2 - *p* - *nitrobenzyloxycarbonylaminoethyl*)*thiovinyl*] - 2 -

azetidinone **20**. To a soln of **19** (10 mg) in CH_2Cl_2 (2 ml) was added 0.5 ml of CF_3COOH at 0°. After stirring for 10 min at 0°, the reaction mixture was evaporated and dried under reduced pressure to give a residue which was dissolved in CH_2Cl_2 (2 ml). To the resulting soln was added *p*-nitrobenzylchloroformate (60 mg) and 4-dimethylaminopyridine (40 mg), and this was then refluxed for 2 h. The reaction mixture was evaporated and chromatographed on a preparative silica gel tlc plate (developed with cyclohexane/EtOAc = 1/1) to give 1.3 mg of **20** (10.4% yield) as foam: FT ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, d, J = 6.5 Hz), 2.77–2.92 (2H, m), 3.10 (1H, dd, J = 2, 7 Hz, C_3-H), 3.33–3.52 (2H, m), 4.20 (1H, dd, J = 2, 8 Hz, C_4-H), 5.0–5.4 [6H; 5.22 (2H, s), 5.26 (2H, s), NH, CH_3CHOCO], 5.66 (1H, dd, J = 8, 15 Hz), 5.85 (1H, s, NH), 6.24 (1H, d, J = 15 Hz), 7.48–7.60 (4H, m), 8.20–8.30 (4H, m); IR ν_{max} (film) 3330, 1750, 1720 (shoulder), 1610 cm^{-1}.

[3α(*S**),4β(*E*)]- *and* [3α(*S**),4β(*Z*)] - 1 - (tert - *butoxycarbonyl* - *methyl*) - 3 - (1 - *acetoxyethyl*) - 4 - (2 - *chlorovinyl*) - 2 - *azetidinone* **21E** *and* **21Z**. A mixture of stereoisomers **14** (100 mg, 0.218 mmol) in toluene (2 ml) was refluxed for 5 h. Evaporation of the reaction mixture under reduced pressure, and preparative tlc on a silica gel plate (developed with PhH/EtOAc = 3/1) gave 16 mg of **21E** (22% yield, R_f = 0.49) as foam; IR ν_{max} (film) 1770, 1740, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (3H, d, J = 7 Hz), 1.46 (9H, s), 2.03 (3H, s), 3.13 (1H, dd, J = 2.3, 7 Hz), 3.55, 4.11 (2H, AB-q, J = 18.5 Hz), 4.33 (1H, dd, J = 2.3, 8.5 Hz), 5.34 (1H, quintet, J = 7 Hz), 5.98 (1H, dd, J = 8.5, 13 Hz), 6.42 (1H, d, J = 13 Hz): and 8 mg of **21Z** (11% yield, R_f = 0.36) as foam; IR ν_{max} (film) 1770, 1740, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (3H, d, J = 7.5 Hz), 1.48 (9H, s), 2.06 (3H, s), 3.16 (1H, dd, J = 2.5, 7.5 Hz), 3.59, 4.09 (2H, AB-q, J = 18 Hz), 4.78 (1H, dd, J = 2, 9 Hz), 5.38 (1H, quintet, J = 7.5 Hz), 5.92 (1H, dd, J = 7, 9 Hz), 6.38 (1H, d, J = 7 Hz).

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